Coupling of salience and frontal task control networks is related to frontal cortical thinning and executive performance

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Introduction

The coupling of resting state networks (operationalized as the partial correlation of their activity during the scan) may directly reflect pathophysiologic processes or compensatory activity that is related to cognitive impairment. We focus on the correlation of the salience network with the default mode network (DMN) and left and right fronto-parietal task control networks (FPTC-L and FPTC-R). Our hypothesis is that network coupling among salience, DMN and FPTC networks mediates the relationship between cortical thinning and cognitive function.

Does network coupling among salience, DMN and FPTC networks mediate the relationship between cortical thickness and cognitive function?

Methods

Our data are from 53 subjects (ages 68-95, mean age=79, 25 male, 22 with amnestic or other cognitive impairment, 3 demented) from the Adult Changes in Thought neuroimaging cohort. Subjects completed a neuropsychological battery that included the the Mini Mental State Examination (MMSE), the Cognitive Abilities Screening Instrument (CASI), tests of working memory (Digit Span Task), episodic memory (WMS-R Logical Memory), verbal/categorical fluency (Animal and Vegetable naming tests), language dysfunction (Boston Naming Test) and mental processing speed (WAIS-R Digit Symbol; Trail Making Test). The CASI was scaled using item response theory to produce a more accurate measure of general cognition (CASI-IRT[1]). Sample demographics are shown in **Table 1**.

We preprocessed 12 minute resting state scans obtained using a multi-echo acquisition using the AFNI ME-ICA module, which systematically removes artefactual components. We identified regions of interest (ROIs) from published coordinates in attention, salience, and default mode networks, together with primary sensory cortex and basal ganglia.

Using exploratory factor analysis in a structural equation modeling framework, we conducted a factor analysis of the time courses from these ROIs. In this context, a factor is a mathematical description of a structured set of correlated ROIs that operate within larger networks, which we call *network kernels*.[2] Partial correlations of network kernel activity quantify how closely coupled they are in time.

Subject-level network kernel correlations were z-transformed for subsequent statistical analyses. Cortical thickness was assessed using FreeSurfer.

	Mean	SD
Age (years)	78.98	6.11
Male (%)	47%	
Education	17.62	2.75
MMSE	28.34	1.97
WAIS	45.53	10.12
Logical Memory	14.21	4.79
Delayed Recall	12.92	4.78
Boston Naming Test	33.38	18.44
Animals	21.15	4.97
Vegetables	14.34	4.66
TMT-A (s)	30	11
TMT-B (s)	93	52
Trail B minus A (s)	62	46

Table 1. Demographics of sample.

For a mediation relationship between cortical thickness and cognition to hold, network coupling must be correlated to cognition and to cortical thickness. We evaluated these independently. To further investigate whether network kernel correlations mediated the relationship between cortical thinning and cognitive performance, we tested a path model with bootstrapped standard errors using Mplus 7.3.

Results

We identified 11 network kernels (**Figure 1**). Higher FPTC-L/salience coupling was related to lower performance on several neuropsychological measures (MMSE, Digit Span Backward, Trail Making B and B-A, Delayed Recall), controlling for sex, age and years of education (representative scatter plots shown in **Figure 2**).

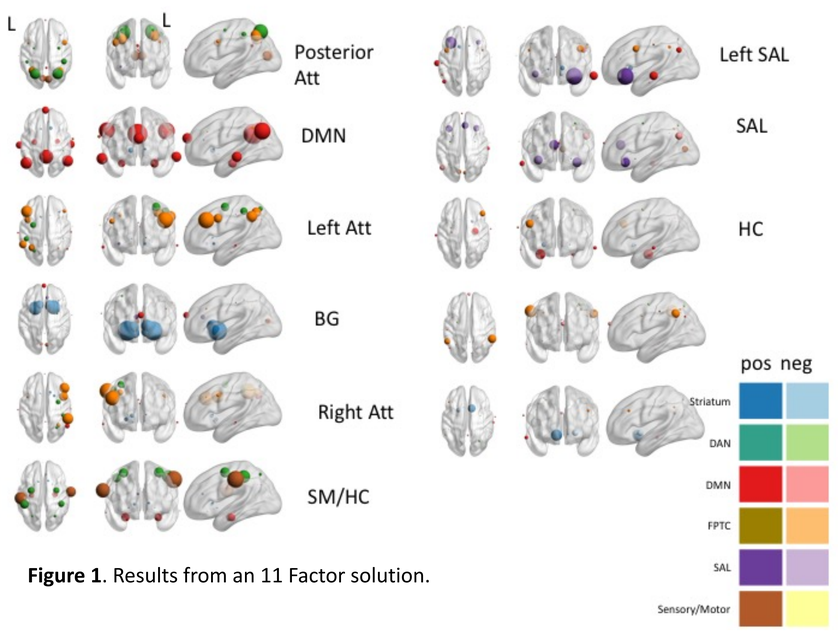

Figure 1. Results from an 11 Factor solution.

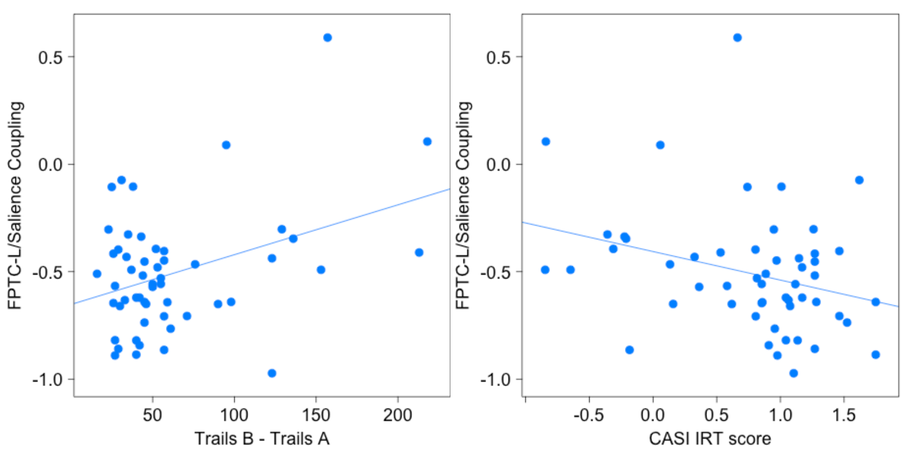

Figure 2. Scatterplot of FPTC-L/Salience coupling and Trails B-Trails A and CASI IRT.

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In contrast, DMN/salience coupling was related only to higher Vegetable naming (p=.033). FPTC-R/salience coupling was not related to any cognitive measures, and was negatively correlated with FPTC-L/salience coupling (*r*=-.65).

Higher FPTC-L/salience and lower FPTC-R coupling was related to a pattern of frontal and insular cortical thinning, controlling for age. **Figure 3** shows the pattern of cortical thinning associated with FPTC-L/salience coupling. DMN/salience coupling was not related to cortical thickness.

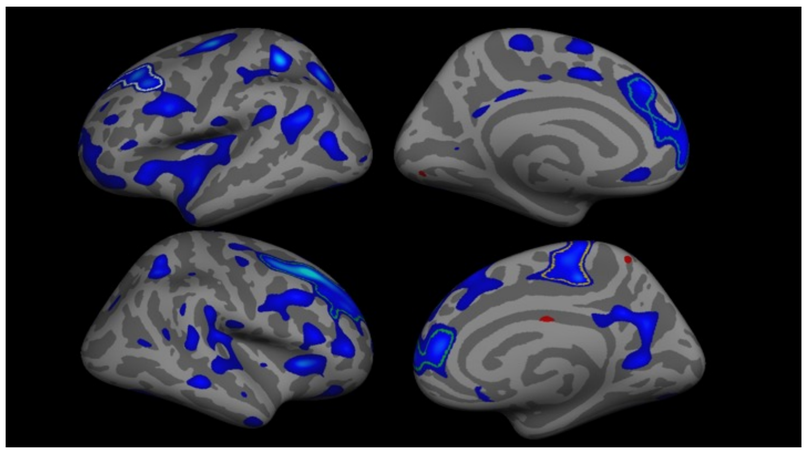

Figure 3. Correlation of FPTC-L/salience coupling to cortical thickness. Clusters significant at p < .05 after cluster correction for multiple comparisons are outlined.

We used the thickness in the right caudal middle frontal parcel as a variable in a mediation analysis (**Figure 4**). There is evidence that higher FPTC-L/salience coupling mediates the relationship between mean right caudal middle frontal cortical thickness and Trail Making B-A, but the indirect effect was only marginally significant (p=.07) in our sample. FPTC-R/salience coupling and DMN/salience coupling do not mediate the relationship between frontal cortical thickness and cognitive function.

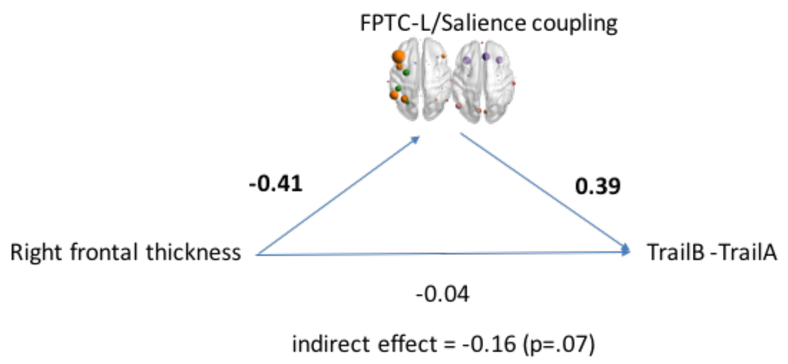

Figure 4. Mediation model. Boldfaced path coefficients are significant at p < .05.

Conclusions

- Executive deficits related to higher FPTC-L/salience coupling are similar to that observed in vascular MCI, and are related to a similar pattern of cortical thinning.
- FPTC-L/salience coupling may mediate the relationship between cortical thinning and executive function, suggesting that coupling of resting state networks may reflect the physiological impact of pathophysiology.
- Confirmatory factor analysis using the network kernel framework will allow us to identify the same networks in an independent sample so that we can see if this finding is replicable.

References

1. Crane PK, van Belle G, Larson EB. Test bias in a cognitive test: differential item functioning in the CASI. Stat Med 2004;23:241-256.
2. Madhyastha TM, Askren MK, Zhang J, Leverenz JB, Montine TJ, Grabowski TJ. Group comparison of spatiotemporal dynamics of intrinsic networks in Parkinson's disease. Brain 2015;138:2672-2686.